DETAILED ACTION

1. The Amendment filed March 22, 2010 in response to the Office Action of September 22, 2009 is acknowledged and has been entered. Previously pending claims 2-4, 8-15, 17, 18 and 20-24 have been cancelled and claims 1, 5, 6, 7, 16, and 19 have been amended. Claims 1, 5, 6, 7, 16, and 19 are currently being examined.

Rejections Maintained
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 1, 5, 6, 7, 16, and 19 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO/2002/059377 (Mack et al. August 1, 2002) for the reasons set forth in section 6 of the Office Action of September 22, 2009, which are set forth below.

WO/2002/059377 teaches detecting at least 6 marker genes comprising estrogen receptor 1, tumor protein p53, matrix metalloproteinase 1, and microtubule associated protein tau which are SEQ ID NOs: 51, 87, 159 and 477, respectively, as being up-regulated in breast tissue compared to normal breast tissue. See Table 4, 9, and 10-pages 4, 5, 114, 192, 194, 195 and 201 of WO/2002/059377 and Tables 1a 1b, 4a, and 4b of the instant specification. WO/2002/059377 and teaches detecting the expression of RAB31, which is a gene in Table 2, is up-regulated in breast tumor tissue compared normal breast tissue. See Table 4- page 115, Table 5-page 141 and 7-page152. WO/2002/059377 teaches detecting these genes for the diagnosis and prognosis of breast cancer. See page 1-lines 14-18, page 4-lines 3-7, page 9-lines 25-28, page 31-lines 1-15, and para. bridging p. 61 and 62. WO/2002/059377 teaches monitoring the efficacy of a therapeutic treatment of breast cancer using the sequences of the invention and different times with screening assays. See p. 5- lines 1-20, p. 7-line 24 to page 8-line 8, page 62-line 18 to page 64-line 18. WO/2002/059377 teaches using the methods to evaluate treatment to determine if a

treatment down regulates tumor growth or recurrence and that the molecular profiling of the invention can be used to diagnose, prognosis, or predictions based on the findings. See para. p. 5-lines 1-20, p.28, and p 61-line 29 to page 62-line 15. Thus, the broadly claimed estimation of the likelihood of success of a given mode of treatment and assessment of whether or not the subject is expected to respond to a given mode of treatment are anticipated by the methods of monitoring the efficacy of a therapeutic treatment, predicting and prognosis of WO/2002/059377 as these methods would inherently be comprised by the broadly claimed steps of estimation and assessment of claims 6 and 7. US Pat. App. Pub. 2004/0029114 teaches using predictive algorithms. See page 11-line 22 to page 13- line 30 and Table 25-page 347. WO/2002/059377 teaches kits with primers and probes for detecting the markers of the invention. See page 92-line 16 to page 93-line12 and p. 52-lines18-26.

Applicants argue that the rejection of claims 1, 3, 5-8, 16, 18 and 19 under 35 U.S.C. § 102 (b) as anticipated by WO/2002/059377 (Mack I) and under 35 U.S.C. § 102 (e) as anticipated by US Pat. Pub. 2004/0029114 A1 (Mack II) is respectfully traversed. Neither Mack I or Mack II teach or suggest a method as claimed in Claims 1 and 19 which include the particular combination of the four markers claimed. Mack I and II disclose a wide variety of marker genes, but not the claimed combination. Accordingly, the rejection is improper and should be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive because the comprising language of the claims (see preamble of claims 1 and 19) allows for the examination of other marker genes in addition to the particular combination of the four markers claimed, of which Mack I determines the expression.

3. Claims 1, 5, 6, 7, 16, and 19 remain rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. App. Pub. 2004/0029114 A1 (Mack et al. Jan. 24, 2001) for the reasons set forth in section 7 of the Office Action of September 22, 2009, which are set forth below.

US Pat. App. Pub. 2004/0029114 A1 teaches detecting at least 6 marker genes comprising estrogen receptor 1, tumor protein p53, matrix metalloproteinase 1, and microtubule associated protein tau which are SEQ ID NOs: 51, 87, 159 and 477, respectively, as being up-

regulated in breast tissue compared to normal breast tissue. See paragraphs 0009-0023, Table 4, 9, and 10 pages 49, 120, 121, 122 and 127 and Tables 1a 1b, 4a, and 4b of the instant specification. US Pat. App. Pub. 2004/0029114 A1 teaches detecting the expression of RAB31 is up-regulated in breast tumor tissue compared normal breast tissue. See Table 4 page 50 and Table 5-page 75. US Pat. App. Pub. 2004/0029114 A1 teaches using these methods for the diagnosis and prognosis of breast cancer. See 0002, 0009, 0055, 0115, and 0221. US Pat. App. Pub. 2004/0029114 A1 teaches monitoring the efficacy of a therapeutic treatment of breast cancer using the sequences of the invention and different times with screening assays. See para. 0021-0023, 0044-0047, 0224-0231. US Pat. App. Pub. 2004/0029114 A1 teaches using the methods to evaluate treatment to determine if a treatment down regulates tumor growth or recurrence and that the molecular profiling of the invention can be used to diagnose, prognosis, or predictions based on the findings. See para. 0021-0023, 0106, 0221 and 0222. Thus, the broadly claimed estimation of the likelihood of success of a given mode of treatment and assessment of whether or not the subject is expected to respond to a given mode of treatment are anticipated by the methods of monitoring the efficacy of a therapeutic treatment, predicting and prognosis of US Pat. App. Pub. 2004/0029114 as these methods would inherently be comprised by the broadly claimed steps of estimation and assessment of claims 6 and 7. US Pat. App. Pub. 2004/0029114 teaches using predictive algorithms. See para. 0062-066 and Table 25-page 246. US Pat. App. Pub. 2004/0029114 teaches kits with primers and probes for the markers of the invention. See para. 0346-0348 and 0193.

Applicants argue that the rejection of claims 1, 3, 5-8, 16, 18 and 19 under 35 U.S.C. § 102 (b) as anticipated by WO/2002/059377 (Mack I) and under 35 U.S.C. § 102 (e) as anticipated by US Pat. Pub. 2004/0029114 A1 (Mack II) is respectfully traversed. Neither Mack I or Mack II teach or suggest a method as claimed in Claims 1 and 19 which include the particular combination of the four markers claimed. Mack I and II disclose a wide variety of marker genes, but not the claimed combination. Accordingly, the rejection is improper and should be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive because the comprising language of the claims (see preamble of claims 1 and 19) allows for the examination of other marker genes in addition to the particular combination of the four markers claimed, of which Mack II determines the expression.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WO/2002/059377 (Mack et al. August 1, 2002) as applied to claim 1, 3, 5-8, 16, 18 and 19 above, and in view of US Pat. App. Pub. 2003/0224374 A1 (Dai et al. June 18, 2001) for the reasons set forth in section 8 of the Office Action of September 22, 2009, which are set forth below.

It is noted that claim 16 for the instant rejection is alternatively being examined as drawn to the elected species SEQ ID NO: 4 from Table 2.

WO/2002/059377 teaches as set forth above, but does not teach determining the expression of SEQ ID NO: 4 from Table 2 or using a Support Vector Machine predictive algorithm.

US Pat. App. Pub. 2003/0224374 A1 teaches comparing the expression at least 6 marker genes comprising the estrogen receptor 1/NM_00125, tumor protein p53, matrix metalloproteinase 1/NM_002421, and NM_00226, which are SEQ ID NOs: 51, 87, 159, and 4 respectively, for the prognosis and diagnosis of breast cancer. See Table 1, para. 0003, 0006, 0012, 0013, 0020, and 0021 and Tables 1a 1b, 4a, and 4b of the instant specification.

US Pat App. Pub. 2003/0198972 teaches that karyopherin alpha 2 (KPNA2, RAG cohort 1, importin alpha), which is SEQ ID NO: 4 is increased in Grade III breast cancer samples. See Abstract, para.0107, Table 6 and 9 and 2 of the instant specification.

It would have been *prima facie* obvious at the time the invention was made and one of skill in the art would have been motivated to further examine the expression of karyopherin alpha 2 (KPNA2, RAG cohort 1, importin alpha), which is SEQ ID NO: 4, in combination with the breast cancer markers examined by WO/2002/059377 for the diagnosis and characterization of breast cancer because KPNA2/SEQ ID NO: 4 had been independently identified by US Pat. App. Pub. 2003/0224374 A1 and US Pat App. Pub. 2003/0198972 as being involved in breast cancer development and being a marker thereof. Thus, one of skill in the art would have been motivated to examine the expression of KPNA2/SEQ ID NO: 4 to confirm and validate the results found with other breast cancer markers and increase the significance of the test. Given that the methods of determining the expression of these genes were well known in the art, one of skill in the art would have had a reasonable expectation of success of performing the claimed methods.

Applicants argue that the rejection of claims 9 and 16 under 35 U.S.C. § 103(a) for obviousness over Mack I in view of US Pat. App. Pub. 2003/0224374 A1 (Dai), and further in view of US Pat. App. Pub 2003/0198972 (Erlander I) and US Pat. App. Pub. 2004/0002067 A1 (Erlander II) is respectfully traversed.

Applicants argue that none of the references disclose or suggest the particular cited combination of marker genes as claimed. Accordingly, the rejection is improper and should be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive because the comprising language of the claims (see preamble of claims 1 and 19) allows for the

examination of other marker genes in addition to the particular combination of the four markers claimed, of which Mack I determines the expression. Thus, in view of the combined teachings of the references, additionally, examining the expression of KPNA2/SEQ ID NO: 4 with the markers of Mack I would have been *prima facie* obvious to confirm and validate the results found with other breast cancer markers and increase the significance of the test, as previously set forth.

5. All other objections and rejections recited in the Office Action of September 22, 2009 are withdrawn.

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642